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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/604,876	06/28/2000	Mercy M. Davidson	0575/56614/JPW/JML/HA	6365

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Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/08/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/604,876	Davidson
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 25, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 8-10, and 12-18* is/are pending in the application.

4a) Of the above, claim(s) *13-18* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 8-10, and 12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 21, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 10 on 2/25/03 (certificate of mailing for 2/20/03).

Claims 1, 3-5, 8-10, and 12-18 remain pending in the application. Claims 13-18 were withdrawn from consideration in Paper No. 7 as being drawn to a non-elected invention. Applicant timely traversed the restriction requirement which was subsequently made final.

Claims 1, 3-5, 8-10 and 12 are under consideration in this Office Action.

Objections Withdrawn

Applicant's amendments were sufficient to overcome the objection to "Dubeco's minor essential medium" at page 17, line 9 of the specification, and the objection to claims 8-10 and 12 for being ungrammatical.

Rejections Withdrawn

Applicant's amendments were sufficient to overcome the rejection of claims 8-10 and 12 under 35 USC 112, first paragraph for lack of enablement regarding incapacity to perform glycolysis is due to depletion of mitochondrial DNA. These claims are now rejected under 35 USC 112, first paragraph on new grounds, see below.

Claim Rejections - 35 USC § 112

Claims 1, 3-5, 8-10 and 12 and rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an undifferentiated immortalized cell line which is the product of a fusion of a human postmitotic primary non-immortalized cardiomyocyte with a human fibroblast that lacks mitochondrial DNA and comprises a vector for the expression in fibroblasts of [redacted] that immortalizes fibroblasts wherein the vector is replicable in fibroblasts, wherein the cells express beta myosin heavy chain, desmin, and connexin-43, and while being enabling for methods of making an undifferentiated immortalized human cell line by fusing a primary post-mitotic human cell with a human fibroblast that lacks mitochondrial DNA and comprises a vector for the expression in fibroblasts of an oncogene that immortalizes fibroblasts wherein the vector is replicable in fibroblasts, does not reasonably provide enablement for the broader scope of any immortalized human cardiomyocyte cell line, and does not provide enablement for methods of making immortalized cell lines using replicable vectors conferring immortality other than vectors that express oncogenes that immortalize fibroblasts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

RS 5/8/03

SV40 large T antigen

Claims 1 and 3-5 are drawn to immortalized human cardiomyocyte cell lines made by fusing a human postmitotic primary non-immortalized cardiomyocyte with a fibroblast that lacks mitochondrial DNA and comprises a replicable vector that confers immortality on any cell comprising it. The scope of immortalized human cardiomyocyte cell lines recited in the preamble

is not limited, and could be construed to embrace differentiated cardiomyocytes that express action potentials and display a beating phenotype.

The specification asserts that these cells are useful for treating damaged cardiac tissue (page 6, line 20), and for screening substances that inhibit or enhance cardiomyocyte functions including electrophysiological, biochemical, and molecular genetic functions. Enablement of the claimed cells will be considered in light of these asserted uses.

The prior art taught an immortalized mouse cardiomyocyte derived from marrow stromal cells. See Makino et al (J. Clin. Invest 103(5): 697-705(1999)). These cells could be differentiated into cells that were connected by intercalated discs to form multinucleated myotubes that showed spontaneous beating. They displayed branching fibers typical of cardiac muscle, had a cardiomyocyte-like ultrastructure, and displayed action potentials. The cells also expressed the cardiomyocyte markers beta myosin, alpha actinin, and desmin, as well as cardiomyocyte-specific transcription factors Nkx2.5/Csx, GATA4, and TEF-1. See entire document, especially abstract. Leiden (J. Clin. Invest 103(5): 591-592(1999)) indicates that the cells of Makino should be useful for studying cardiomyocyte development and function, for identifying cardiac muscle-determining genes, and for studying cardiac promoters. Leiden also remarks on the possibility that these cells could be useful as a source of differentiated cells for the treatment of cardiomyopathies. See paragraph bridging columns 2 and 3 on page 592. Clearly this use is dependent on the ability of these cells to differentiate into cardiac muscle.

The prior art also taught a human fetal cardiac myocyte cell line designated W1 that had been immortalized by transfection with an expression vector for SV-40 large T-antigen. See discussion of Wang et al (1991) below under 35 USC 102 rejections. Wang does not teach that this cell line could be differentiated, and a search of the prior art revealed no evidence that this cell line ever was made to differentiate.

The instant specification exemplifies three cell lines (AC10, AC16, and RL14) that express beta myosin, desmin, and connexin-43, but which are not differentiated, do not contract, and display no action potentials. There is no evidence that the cells express any cardiomyocyte markers other than beta myosin, desmin, and connexin-43. The specification indicates that these cells are de-differentiated by expression of SV-40 large T antigen, and that it may "be possible to induce these cardiomyocytes to differentiate in culture" towards cardiac muscle, but it is clear that this will require further research and may not be possible. See page 22, line 38 to page 23, line 4.

Leiden (1999) indicated that the while questions regarding cardiac myocyte differentiation had been of interest to those of skill in the art for over 20 years, prior to the publication of Makino (1999) there was no cell line available that could be differentiated into committed cardiomyocytes and used as an in vitro model to study these questions. See page 591, column 1, lines 1-8, and paragraph bridging pages 591 and 592. It may be inferred then that the immortalized human fetal cardiac myocyte cell line developed by Wang in 1991 was not suitable for these purposes. Presumably this was due to the fact that these cells were not shown to be differentiatable. Thus the prior art teaches that immortalized cardiomyocytes could be potentially

useful for the study of cardiac myocyte differentiation or the treatment of cardiomyopathies if they could be made to differentiate into committed cardiomyocytes. However, the evidence of record indicates that human cardiomyocytes expressing SV-40 large T antigen cannot differentiate into committed cardiomyocytes. The instant specification teaches no example of any differentiated immortalized human cardiomyocyte and fails to provide the guidance that is missing from the prior art as to how to cause the exemplified cells to differentiate. So, one of skill in the art would have to perform undue experimentation in order to make immortalized human cardiomyocytes that express SV-40 large T antigen and that can be differentiated to beat, display action potentials, and display other characteristic of differentiated cardiomyocytes such as the expression of alpha actinin, and cardiomyocyte-specific transcription factors, such as are embraced by the instant claims.

Because the exemplified cells express beta myosin heavy chain, desmin, and connexin-43, and it would be of interest to identify compounds that affect the expression of these proteins, the specification is considered to be enabled for an undifferentiated immortalized cell line which is the product of a fusion of a human postmitotic primary non-immortalized cardiomyocyte with a human fibroblast that lacks mitochondrial DNA and comprises a vector for the expression in fibroblasts of SV-40 large T-antigen that is replicable in fibroblasts, wherein the cells express beta myosin heavy chain, desmin, and connexin-43.

Claims 8-10 and 12 are drawn to methods of making a human immortalized cell line derived from a post mitotic primary cell culture. The method requires fusion of a post mitotic

primary cell with a fibroblast that comprises a replicable nucleic acid vector that immortalized the fibroblast cell line. The scope of replicable nucleic acid vectors that can immortalize cells is no limited, and this is the issue under consideration in this part of the rejection. Claims 1 and 3-5 also require the use of such a vector, so this portion of the rejection applies to these claims as well.

The specification exemplifies a replicable vector expressing SV40 large T antigen, but teaches no other type of replicable vector that can effect transformation of fibroblasts.

A search of the prior art revealed no class replicable vectors that can be used to immortalize cells per se. Rather the ability to immortalize cells depends upon genes encoded by the vectors. Because the specification exemplifies no replicable vector capable of immortalizing fibroblasts other than ones encoding SV-40 large T antigen, the enabled scope is limited to such vectors.

Written Description

Claims 1, 3-5, 8-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention embraces the genus of replicable vectors that confer immortality on a cell.

The specification exemplifies a single species of the genus.

The specification provides no correlation between any specific structural determinant of the vector, i.e. any gene, and the required function of conferring immortality. The specification fails to describe any other species of the genus by structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Thus one of skill in the art could not conclude that applicant was in possession of the claimed genus at the time of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-5 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al (In Vitro Cellular and Developmental Biology 27(1): 63-74, 1/1991).

Wang teaches a human fetal cardiac myocyte cell line designated W1. This line is considered to be immortalized because it was maintained in culture for one year. See abstract. Claims 3-5 are included in the rejection because there is no apparent difference between these cells and the W1 line. For example, like the cells of claims 3-5, the W1 cells carry an expression

construct encoding SV40 T antigen (pRSVTAg). See page 67, column 2, last complete sentence. The specification teaches that the cells of claims 3-5 express beta-myosin heavy chain, connexin-43, and desmin. Wang is silent as to whether or not the W1 cells express these markers. However, expression of these proteins is considered to be an inherent characteristic of cardiomyocytes, and is therefore considered to occur in the W1 cells absent evidence to the contrary. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Arguments

Applicant's arguments filed 2/2503 have been fully considered but they are not persuasive.

Applicant argues that Wang fails to teach each and every feature of the claimed cell lines. This argument is unpersuasive because it lacks any support. It is not clear that there is any difference between the cell line of Wang and the claimed lines. The cell line of Wang carries an expression construct encoding SV40 T antigen as do the instant cells, and expresses a cardiac myosin as do the claimed cells. See Table 2 of Wang and page 20, lines 9 and 10 of the

specification.. There is no evidence that the claimed cells differ from those of Wang by expressing any fibroblast marker (see page 20, lines 2 and 3). Because the PTO does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, and because Applicant has failed to point to any specific difference between the cell lines, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER